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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
08/981272	KIPPS
Examiner	**Art Unit**
GAMBEL	1644

Office Action Summary

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 8/20/01 / 11/29/00 / 3/19/00

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 11-66, 68-84, 87-90, 92-111, 113-122, 137-140

4a) Of the above claim(s) _____ is/are withdrawn from consideration. 11-66, 68-84, 110, 116-122

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 87-90, 92-111, 113-115, 137-140

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner. SEE OFFICE ACTION

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☑ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 8/19/02 (Paper No. 29), has been entered.
Claims 111 has been amended.
Claims 139-140 have been added.

Claims 11-66, 68-82, 87-90, 92-111, 113-122 and 137-140 are pending.

Claims 1-10, 67 and 83-86, 91, 112 and 123-136 have been canceled previously

Applicant's election with traverse of Group I wherein a nucleic acid sequence encoding a murine CD40 ligand is introduced into a CD40$^+$ cell, wherein the CD40L specificity is murine CD40L, corresponding to claims 87/88, wherein the domain/subdomain of the non-human CD40 ligand comprise Domain IV, corresponding to claims 92/95, wherein the nucleic acid comprises SEQ ID NO: 3, and wherein the cell is a CLL cell correspond to claims 111/114 in Paper No. 29 is acknowledged.

The traversal is on the ground(s) that this Restriction Requirement that these claims are directed to generic claims and a reasonable number of species claims. This is not found persuasive because of the reasons of record set forth in their previous Office Actions. For example, the inventions are independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed (see MPEP 806.05-806.05(I))) for the reasons of record. Also, the inventions require non-coextensive searches whether or not the classifications alone are coextensive. As indicated previously, claims drawn to methods of expressing CD40L or increasing the concentration of CD40L in cells by transfecting chimeric CD40L molecules which comprise both murine and human CD40L as well as CD40L and TNF-alpha, TNF-beta, Fas ligand, CD70, CD30 ligand, 4-1BBL, Nerve growth factor beta and TRAIL, previously not elected and/or not claimed have been withdrawn from consideration. These claims are drawn to transfected chimeric molecules which differ in structure and function and which are distinct from the originally elected invention of methods which relied upon transfecting CD40L alone.

The requirement is still deemed proper and is therefore made FINAL.

Applicant admits that murine CD40L and human CD40L are obvious variants of one another.

As indicated below, it appears that there was insufficient motivation to incorporate the combination of both mouse and human CD40L elements into a CD40 expressing cell, including CLL cells at the time the invention was made.

However, given that certain claims do read on the introduction of human CD40L into CD40 expressing cells, including CLL cells, prior art has been applied as it reads on the elected invention of human CD40L.

As indicated previously, claims 11-66, 68-82, 110 and 116-122 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to the nonelected inventions and/or species.

In the interest of compact prosecution, claims 87-90, 92-111, 113-115 and 137-140 are under consideration in the instant application s they read on the elected Group and species as well as to advance prosecution those claims which read on introducing the combination of both mouse and human CD40L into CD40 expressing cells.

2. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

3. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 87-90, 92-109, 111, 113-115 and 137-140 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is noted that this is a written description rejection under 35 U.S.C. 112, first paragraph

The claims are directed to "a CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand", which do not meet the written description provision of 35 USC 112, first paragraph. There is insufficient guidance and direction as to the written description of "a CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" intended and encompassed by the claimed methods.

For example, page 24 of the specification discloses that the present invention contemplates the use of accessory molecules such as CD40L which is homologous to a particular SEQ ID NO and thus hybridizes to this sequence present at low stringency hybridization conditions.

Pages 24-25 of the specification discloses that the size of a particular segment derived from the differencd accessory molecule ligand genes may vary from a nucleotide sequence encoding a few amino acids, a sub-domain of the accessory molecule ligand, a domain of the accessory molecule ligand or more than a domain of an accessory molecule ligand.

While the specification discloses "CD40 as "the CD40 ligand receptor", there appears insufficient written description for any "CD40 ligand receptor".

While the specification discloses human, mouse and bovine CD40L, there appears insufficient written description for any "non-human CD40 ligand", including homologous sequences to human and mouse as well as "non-human CD40 ligand" under low stringency hybridization conditions.

While the specification discloses the domain structure, particularly Domains I, II, III and IV of human, mouse and bovine CD40 ligand, there appears insufficient written description of domains other than Domains I, II, III and IV set forth in Table I and there does not appear sufficient written description of subdomains.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed "members of the tumor necrosis factor family" and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. For example the nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicant is claiming very broad generic classes of molecules encompassing "a CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" based upon the support of the disclosure of a limited representative number of species (e.g. CD40 as the "CD40 ligand receptor"; specific SEQ ID NOS for mouse and bovine CD40L; and domains I, II, III and IV). The instant invention encompasses any "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand", yet the instant specification does not provide sufficient written description as to the critical structural features of the recited "limitations" and the correlation between the chemical structure and the desired structural and/or function.

Applicant is relying upon certain structural and/or biological activities and the disclosure of a limited representative number of species to support an entire genus / genuses. The reliance on the disclosed limited examples of a particular member(s) of the "a CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" does not support the written description of any "member" of these "molecules".

For example, it has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities.

Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

The instant specification and claims do not provide sufficient functional characteristics coupled with a known or disclosed correlation between function and structure. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus / genuses, and because the genus / genuses is / can be highly variable, the disclosure of a particular "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" is insufficient to describe the genus of molecules, encompassed by the claimed invention.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a nucleic acid encoding a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved, and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting a polypeptide structure from the disclosure of a limited sequence or a limited number of molecules disclosed in the specification as-filed and, in turn, utilizing predicted structural determinations to ascertain binding or functional aspects of the claimed "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" and finally what changes can be tolerated with respect thereto is complex.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences for increasing the stability on the surface of the cell relative to that of a human CD40 ligand, for example. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for increasing the stability on the surface of the cell relative to that of a human CD40 ligand, for example. A person of skill in the art could not envision which particular nucleic acids encoding amino acid sequences of "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" are essential and could be used in methods of expressing a CD40 ligand in a human cell and, in turn, which nucleic acids encoding "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" for increasing the stability on the surface of the cell relative to that of a human CD40 ligand

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) disclose that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus an assignment of function based upon sequence homology or identity without further functional analysis does not appear to provide sufficient written description for the claimed "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" encoding nucleic acids.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

In the absence of structural characteristics that are shared by members of the genus / genuses of "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand", one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus / genuses. Thus, applicant was not in possession of the claimed genus / genuses. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 87-90, 92-109, 111, 113-115 and 137-140 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "CD40" as the CD40 ligand receptor" and for certain combinations of mouse and human "CD40L" and certain "domains" thereof for expressing CD40 ligand into human CD40 ligand receptor bearing cells, does not reasonably provide enablement for any "CD40 ligand receptor" and for an non-human CD40 ligand" and "domain and/or subdomains thereof" that would enable the expression of CD40 ligand in a human cell, including increasing the stability on the surface of the cell relative to that of a human CD40 ligand.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to the enablement of any "CD40 ligand receptor", "domain or subdomain" of "non-human CD40 ligand" intended and encompassed by the claimed methods.

For example, page 24 of the specification discloses that the present invention contemplated the use of accessory molecules such as CD40L which is homologous to a particular SEQ ID NO and thus hybridizes to this sequence present at low stringency hybridization conditions.

Pages 24-25 of the specification discloses that the size of a particular segment derived from the different accessory molecule ligand gene may vary from a nucleotide sequence encoding a few amino acids, a sub-domain of the accessory molecule ligand, a domain of the accessory molecule ligand or more than a domain of an accessory molecule ligand.

While the specification discloses "CD40 as "the CD40 ligand receptor", there appears insufficient enablement for any "CD40 ligand receptor". Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies "CD40 ligand receptors" other than "CD40".

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. domain and subdomains of CD40 ligand) by expressing or increasing the concentration and/or increasing the stability of CD40 ligand on CD40 expressing cells requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting the ability of various domains and subdomains of any CD40 ligand to enable the expression or increased stability of CD40 ligand on a CD40 expressing cells from the limited examples disclosed in the specification as filed, and in turn, utilizing predicted structural determinations to ascertain the expression and functional aspects of CD40 ligand, and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

The skilled artisan would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance based on in vitro characterization assays to direct a person of skill in the art to select particular sequences as essential for in vivo characterization of their ability to express or increase the concentration and/or increase the stability of CD40 ligand on CD40 expressing cells.

In re Fisher, 166 USPQ 18 (CCPA 1970). indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. The relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "domains" and particularly "subdomains"' with the ability to express or increase the concentration and/or increase the stability of CD40 ligand on CD40 expressing cells. Without sufficient guidance, the changes which can be made in the structure of "domains" and "subdomains" or CD40 ligand, including any non-human CD40 ligand and still provide for increased stability and the ability to increase the expression of CD40 ligand in human cells is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant is invited to amend the claims to recite "CD40" as the "CD40 ligand receptor"; to recite the specific enabled domains I, II, III and IV, as appropriate; and to recite the specific SEQ ID NOS. Of the particular enabled "non-human CD40L" based upon the support of the instant disclosure .

9. Claims 87-90, 92-111, 113-115 and 137-140 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 92-93, 103-109, 111, 113-115 and 137-140 are indefinite in its recitation of "extracellular" "domain" and subdomain"' because these "terms"' are not defined by the claim, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Also, it is noted that specification discloses both proximal and distal extracellular domains and the claims are ambiguous as to the metes and bounds of the claimed extracellular domains.

With respect to "domain", applicant is invited to amend the claims to recite domains I, II, III and IV and indicated that the domains I, II, III and IV are those disclosed in Table 1 of the specification for defining the metes and bounds of the claimed "domains". Alternatively, applicant may amend the claims to recite specific amino acid residues.

B) Claims 90, 92-102 and 111 are indefinite because the antecedent basis for the recitation of the "encoded CD40 ligand" in claim 90, line 5 is ambiguous (e.g. "human CD40 ligand" or "non-human CD40 ligand").

C) Given applicant's election of CD40L, claims 108 -109, 111, 113-114 are indefinite in its recitation since it appears that the claimed method comprising introducing a nucleic acid sequence encoding a domain or subdomain of human CD40 ligand and a domain or subdomain of a human CD40 ligand. Therefore, the claimed method is ambiguous as it appears human CD40L is being introduced twice in a human cell.

For examination purposes, these claims are being examined as if the ordinary artisan is simply introducing CD40L into a human cell expressing a CD40 ligand receptor (i.e. CD40).

D) Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 108 -109 are rejected under 35 U.S.C. § 102(e) as being anticipated by Maraskovsky et al. (U.S. Patent No. 6,017,572) (see entire document) (of record).

Maraskovsky et al. teach transfecting human dendritic cells with CD40L and modifications thereof to augment responses to desired antigens (see entire document, including Summary of the Invention, Detailed Description of the Invention, particularly column 11, paragraph 4). Dendritic cells are CD40 expressing cells. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods.

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03. Therefore, the prior art CD40L comprises Domain IV.

It is noted that one of the elected species is CLL (versus dendritic cells). Given that Maraskovsky et al. (U.S. Patent No. 6,017,572) is being applied in the rejection under 35 U.S.C. § 103(a) and in the interest of compact prosecution, Maraskovsky et al. has been applied herein under 35 U.S.C. § 102(e).

As pointed out above, these claims are indefinite in that it is not clear whether the recitation reads on introducing a single human CD40L ~~(and~~ domains thereof) or two different human CD40L (and domains thereof). Even if it reads on introducing two different domains of human CD40L, the prior art applies, given the "comprising" language.

9. Claims 108 -109, 111, 113-114 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Freeman et al. (U.S. Patent No. 5,861,310) in view of Yellin et al. (J. Immunol., 1994) and Alderson et al. (J. Exp. Med. 178: 669-674, 1993) ,Spriggs et al. (U.S. Patent No. 6,016,832), Maraskovsky et al. (U.S. Patent No. 6,017,572) as well as pages 40-53 of the instant specification which acknowledges that the general methods of providing chimeric/gene therapy constructs as well as manipulating cells were known and practiced at the time the invention was made for the reasons of record.

Freeman et al. teach altering the reactivity of a cell and treating human neoplasia by introducing a gene encoding an accessory molecule ligand (B7) alone or together, that is to be expressed on a cell surface, including tumor cells (see entire document).

Freeman et al. differs from the instant elected invention by not disclosing CD40 ligand as a costimulatory or accessory molecule to be introduced into CD40 expressing CLL cells.

Yellin et al. teach that transfecting cells with CD40 ligand enhances a cell costimulatory activity, including the priming and clonal expansion of antigen specific T cells as well as providing helper function for cytotoxic T cell responses (see entire document, including the Abstract and Discussion). Yellin et al. teach that B-CLL cells respond to CD40L, wherein said cells manifest enhanced costimulatory activity (see Results and Discussion). Yellin et al. also can conceive of therapeutic strategies on the basis of induction of CD80 expression on B-CLL cells by CD40L signals in the hopes of inducing an anti-B-CLL T cell response (see page 673, column 1, lines 2-6).

CLL cells are CD40 expressing cells.

Alderson et al. teach that CD40 ligand transfected cells induce monocytes to become tumoricidal against human melanoma cells, which indicated that the CD40 ligand had potent biological effects (see entire document, including the Abstract and Discussion). Alderson et al. teach transfection with either murine or human CD40 ligand (for example, see page 671).

Spriggs et al. (U.S. Patent No. 6,016,832) and Maraskovsky et al. (U.S. Patent No. 6,017,572) have been added as additional teachings of transfecting various human cell types with CD40L and modifications of said CD4OL to provide the biological activity of CD40L in order to stimulate immune responses (see entire document, including Sections indicated above).

Therefore, it would have been prima obvious to the ordinary artisan at the time the invention was made to substitute the potent costimulatory/accessory molecule properties of the CD40 ligand into the methods of Freeman et al. to alter the immunoreactivity of cells, including CLL tumor cells, that is, to increase antigen presentation and/or immunoreactivity. The claimed limitations encompassing chimeric genes and vectors were known and practiced by the ordinary artisan at the time the invention was made, as evidenced by Freeman et al. Pages 40-53 of the instant specification also acknowledges that the general methods of providing chimeric/gene therapy constructs as well as manipulating cells for were known and practiced at the time the invention was made.

One of ordinary skill in the art at the time the invention was made would have been motivated to select CD40 ligand as an accessory molecule ligand to express in cells, including CD40 expressing CLL tumor cells, to increase their immunoreactivity. Given that the claims read on the expression of Domain IV, which was an extracellular domain, which provided providing binding to its ligand CD40, then it would have been obvious to make sure that CLL cells expressed the ligand binding domain(s) of CD40L in order to stimulate appropriate responses. As pointed out above, even if it reads on introducing two different domains of human CD40L, the prior art applies, given the "comprising" language. Given the combined teachings of the prior art, it would have been expected that the surface markers set forth in claim 102 would have been expressed given the introduction of CD40L into CD40 expressing cells such as CLL.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

It appears that there was insufficient motivation to incorporate the combination of both mouse and human CD40L elements into a CD40 expressing cell, including CLL cells at the time the invention was made.

Applicant is invited to provide claims drawn methods of introducing a combination of mouse and human CD40L elements into CD40 expressing cells, taking into account issues set forth herein under 35 USC 112, first and second paragraphs.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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